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Plasma cortisol delivery from oral cortisol and cortisone acetate: relative bioavailability

V. J. HEAZELWOOD[1], J. P. GALLIGAN[1], G. R. CANNELL[1], F. BOCHNER[2]* & R. H. MORTIMER[1]

[1]Conjoint Internal Medicine Laboratory, Royal Brisbane Hospital and
[2]Department of Medicine, University of Queensland, Brisbane, Queensland, Australia 4029.

1 Plasma cortisol levels were measured before and for 6 h after the intravenous injection of 50 mg cortisol as sodium succinate and oral administration of 50 mg cortisol and 50 mg cortisone acetate in 10 subjects with primary or secondary adrenal failure and in two normal volunteers.

2 Peak cortisol levels of 1518 ± 190 nmol l^{-1} (mean ± s.e. mean) and 739 ± 74 nmol l^{-1} were found 1.46 ± 0.25 and 1.79 ± 0.16 h after oral cortisol and cortisone acetate respectively. The relative bioavailability of oral cortisol and cortisone acetate varied widely (cortisol 26–91%, mean 54 ± 6.9%, cortisone acetate 21–95%, mean 44 ± 6.5%) but despite this wide variation there was, in individual subjects, a highly significant correlation between the bioavailability of the two steroids ($r = 0.870$, $P < 0.001$).

3 This suggests that the wide interindividual variations in plasma cortisol levels seen after oral cortisone acetate are not related to variations in bioconversion of cortisone.

Keywords cortisol cortisone acetate bioavailability

Introduction

Although more potent synthetic glucocorticoids have become available since the therapeutic introduction of cortisone acetate (Hench *et al.*, 1949) this steroid is still widely used as glucocorticoid replacement in patients with adrenal insufficiency. Cortisone is biologically inactive until 11β hydroxylated to form cortisol and its clinical use has been questioned because of possible problems in absorption and bioconversion (Besser & Edwards, 1972). We had noted in some patients a poor clinical response to conventional doses of cortisone acetate, and, as little information is available about the bioavailability of this steroid, we have examined the subject further.

Methods

We studied 10 patients with primary or secondary adrenal failure, confirmed by conventional endocrine investigations, and two normal volunteers (Table 1). All gave informed consent. No subject had clinical or biochemical evidence of hepatic or renal disease and none was taking drugs known to alter plasma levels of cortisol binding globulin or to induce mixed function oxidases. Patients with adrenal insufficiency had been taking cortisone acetate in doses of approximately 25 mg/m^2 surface area daily for at least 1 year until 16.00 h on the day before the study. The normal subjects were each given 2 mg dexamethasone orally at 23.00 h before each study to suppress endogenous cortisol secretion.

Each fasting subject was randomly given, at 08.00 h on different days, 50 mg cortisol as the sodium succinate (Efcortelan, Glaxo) intravenously, 10 × 5 mg tablets of cortisol (Hydrocortone, Merck Sharpe and Dohme) orally and 44.8 mg cortisone as 10 × 5 mg tablets cortisone acetate (Cortate, Protea) orally. Blood was taken from antecubital venous cannulae before and for 6 h after drug administration. Heparinized blood was immediately centrifuged and the plasma stored at −20°C until estimation of cortisol levels.

*Present address: Department of Clinical Pharmacology, University of Adelaide, Adelaide, Australia.

Table 1 Subject details

Number	*Sex*	*Age (years)*	*Weight (kg)*	*Diagnosis*
1	M	48	74	Addison's disease
2	F	49	67	Addison's disease
3	M	44	65	Addison's disease
4	F	25	49	Addison's disease
5	M	37	65	Addison's disease
6	F	34	64	Pituitary adenoma, bilateral adrenalectomy
7	M	26	90	Pituitary adenoma
8	M	34	56	Idiopathic hypopituitarism
9	M	65	86	Pituitary adenoma
10	M	47	76	Idiopathic hypopituitarism
11	M	28	54	Normal
12	M	40	95	Normal
Mean		39.8	70.0	
s.e. mean		3.35	4.19	

Cortisol was measured by radioimmunoassay using tritiated cortisol and an antibody raised against cortisol-3-oxime-BSA. Cortisone cross reacts with this antibody by 33% but at the low plasma level found after oral cortisone (Colburn *et al.*, 1980) circulating cortisone makes a negligible contribution to measured cortisol levels. The sensitivity of the assay is 10 nmol l^{-1} and the inter-assay coefficient of variation 5.1%. An equation of the form $C = Ae^{-\alpha t} + Be^{-\beta t}$ was computer fitted to the plasma level-time data (Brown & Manno, 1978) and parameter estimates further refined with a modified non linear least squares curve fitting program (Peck & Barrett, 1979). The area under the plasma level-time curve from 0–6 h $AUC_{(0-6)}$ was calculated by trapezoidal rule integration and the area under the curve from 6 h to infinity ($AUC_{6-\infty}$) calculated by dividing the plasma cortisol concentration at 6 h by the terminal elimination rate constant. From the sum of these two areas was subtracted the small contribution due to circulating cortisol present prior to steroid administration. This was calculated by dividing plasma cortisol levels at zero time by the terminal elimination rate constant. Bioavailability, clearance, apparent volume of distribution and plasma half-life were calculated using conventional methods (Gibaldi & Perrier, 1975). The relative bioavailability of cortisone acetate, 50 mg of which contains 44.8 mg cortisone was calculated as:

$$\frac{\text{AUC cortisol after oral cortisone acetate} \times 1.12 \times 100}{\text{AUC cortisol after intravenous cortisol}}$$

This formula assumes a linear dose–AUC relationship over the narrow dose range 44.8–50 mg cortisone. Statistical methods included the paired-sample *t* and bivariate regression and correlation tests (Zar, 1974). In the text, means are expressed ± s.e. mean.

Results

Mean plasma cortisol levels prior to drug ingestion were low (78 ± 8 nmol l^{-1}). Mean plasma cortisol levels after intravenous and oral cortisol and oral cortisone acetate are shown in Figure 1. Maximal (C_{max}) cortisol levels after oral

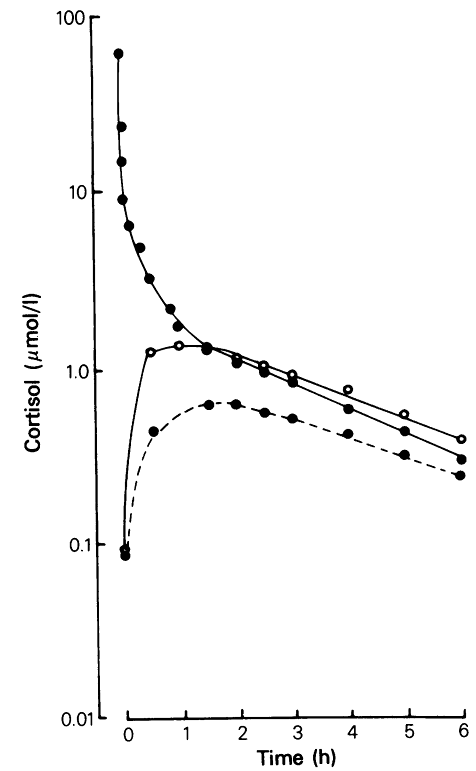

Figure 1 Mean plasma cortisol levels after cortisol sodium succinate 50 mg i.v. (●——●), cortisol 50 mg p.o. (○——○) and cortisone acetate 50 mg p.o. (●- - -●).

Table 2 Kinetic data i.v. cortisol

Number	*CL* ($l\,kg^{-1}h^{-1}$)	k (h^{-1})	$t_{1/2}$ (h)	V_z ($l\,kg^{-1}$)
1	0.159	0.2618	2.65	0.606
2	0.271	1.1030	0.63	0.246
3	0.129	0.3388	2.05	0.382
4	0.196	0.6176	1.12	0.318
5	0.139	0.1917	3.62	0.725
6	0.210	0.9366	0.74	0.225
7	0.327	0.8983	0.77	0.364
8	0.105	1.5207	0.46	0.069
9	0.131	0.3617	1.92	0.363
10	0.298	0.4860	1.43	0.613
11	0.207	·0.3271	2.12	0.633
12	0.202	0.6106	1.14	0.331
Mean	0.198	0.6378	1.55	0.406
s.e. mean	0.020	0.1161	0.27	0.057

Table 3 Kinetic data p.o. cortisol

Number	*CL* ($l\,kg^{-1}h^{-1}$)	k (h^{-1})	$t_{1/2}$ (h)	V_z ($l\,kg^{-1}$)	k_a (h^{-1})
1	0.380	0.6722	1.03	0.565	0.8312
2	0.319	0.3239	2.14	0.986	0.4019
3	0.362	0.5677	1.22	0.638	0.6895
4	0.496	0.4064	1.71	1.221	3.2917
5	0.543	0.6687	1.04	0.812	0.7714
6	0.231	0.5143	1.35	0.449	0.5857
7	0.437	0.4031	1.72	1.083	0.4239
8	0.297	0.6303	1.10	0.471	0.7643
9	0.344	0.6261	1.11	0.549	0.7936
10	0.433	0.8672	0.80	0.500	1.1206
11	0.250	0.3918	1.77	0.639	0.4449
12	0.584	0.7206	0.96	0.810	0.7680
Mean	0.390	0.5660	1.33	0.727	0.9086
s.e. mean	0.032	0.0467	0.12	0.074	0.2246

Table 4 AUC and bioavailability

	AUC (nmol l^{-1} h)			*Bioavailability (%)*	
Number	*i.v. cortisol*	*p.o. cortisol*	*p.o. cortisone*	*p.o. cortisol*	*p.o.* cortisone*
1	11742	4905	3782	41.8	36.1
2	7585	6449	6428	85.0	94.9
3	16402	5862	3199	35.7	21.8
4	14340	5672	2643	39.6	20.6
5	15273	3907	2948	25.6	21.6
6	10242	9334	6439	91.1	70.4
7	4691	3511	1905	74.9	45.5
8	23432	8296	5648	35.4	27.0
9	12202	4666	4802	38.2	44.1
10	6097	4188	2648	68.7	48.6
11	12333	10204	6806	82.7	61.8
12	7196	2488	2069	34.6	32.2
Mean	11795	5790	4109	54.4	43.7
s.e. mean	1507	691	526	6.9	6.6

* Relative bioavailability of cortisone was calculated as described in the methods section.

cortisol (1518 ± 190 nmol l^{-1}) occurred 1.46 ± 0.25 h after dosing and maximal cortisol levels after oral cortisone acetate (739 ± 74 nmol l^{-1}) were found 1.79 ± 0.16 h after tablet ingestion. There is no significant difference between these times. All mean cortisol levels after oral cortisone acetate were significantly (P at least < 0.05) less than those attained after ingestion of oral cortisol. Cortisol pharmacokinetic data are shown in Tables 2 and 3. There was considerable interindividual variation in the AUC of cortisol derived from intravenous cortisol and from oral administration of cortisol and cortisone acetate (Table 4). The contribution to the total AUC of the fraction $AUC_{6-\infty}$ was 5.9 ± 2.0% for i.v. cortisol, 11.3 ± 2.8% for oral cortisol and 13.7 ± 4.4% for cortisone. The bioavailability of oral cortisol was also very variable, ranging from 26–91% (mean 54 ± 6.9%) as was the relative bioavailability of cortisone acetate (range 21–95%, mean 44 ± 6.5%) (Table 4). Despite this wide variation a highly significant (r = 0.870 P < 0.001) correlation was found between the bioavailabilities of the two steroids (Figure 2).

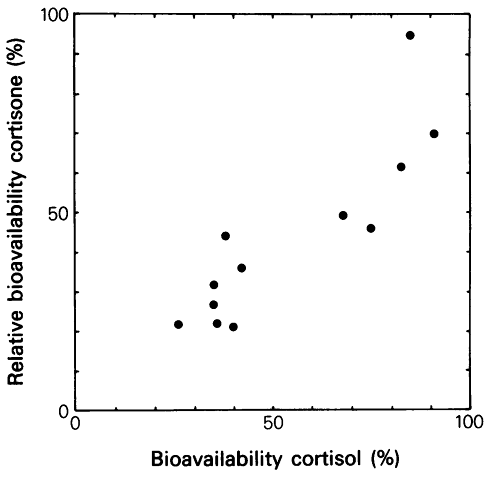

Figure 2 Relationship between the bioavailability of oral cortisol and the relative bioavailability, expressed as cortisol, of oral cortisone acetate. y = −1.27 + 0.826x. r = 0.870, P < .001.

Discussion

Previous reports have demonstrated considerable subject to subject variations in plasma cortisol levels after oral cortisol (Jenkins & Samson, 1967; Kehlet *et al.*, 1976; Fariss *et al.*, 1978; Scott *et al.*, 1978) and after oral cortisone acetate (Jenkins & Samson, 1967; Kehlet *et al.*, 1976; Barbato & Landau, 1977; Fariss *et al.*, 1978; Aanderud & Myking, 1981) even when attempts have been made to correct doses for body weight (Kehlet *et al.*, 1976). Comparison of the two steroids in the same subjects has given conflicting results with cortisol levels achieved after oral cortisone acetate being variously reported as lower (Jenkins & Samson, 1967; Kehlet *et al.*, 1976; Khalid *et al.*, 1982), higher (Barbato & Landau, 1977) or no different (Fariss *et al.*, 1978) to those seen after oral cortisol. The present study confirms that mean cortisol levels are lower after oral cortisone acetate than after cortisol, with the mean bioavailability of cortisone being 80% that of cortisol. This difference is consistent with clinical observations that cortisone acetate has about two thirds the potency of cortisol (Boland, 1952; Ward *et al.*, 1952). The cause of the reduced bioavailability of cortisone relative to that of cortisol is not clear although Jenkins and Samson (1967) have produced evidence that enhanced A ring reduction of cortisone may be important.

The present study demonstrates that very wide interindividual variations in bioavailability exist for oral cortisone acetate and oral cortisol, a degree of variation similar to that reported for prednisone and prednisolone (Davis *et al.*, 1978). Despite this variation the bioavailabilities of cortisone acetate and cortisol in the same subject are closely correlated suggesting that the factors controlling bioavailability are common to both drugs. Thus at least in subjects without hepatic disease, differences in 11β-hydroxylation are probably not an important cause of the marked variations in plasma cortisol levels after oral cortisone acetate. From the clinical therapeutic point of view, the results of this study indicate that a poor clinical response to oral cortisone acetate may be due to poor bioavailability and that substitution of oral cortisol in equivalent dose will not adequately solve the problem. We agree with recommendations (Besser & Edwards, 1972; Kehlet *et al.*, 1976), that measurement of peak cortisol levels after either oral cortisone acetate or cortisol are necessary to adjust glucocorticoid replacement, especially in patients who, despite an apparently adequate steroid dose, have clinical evidence of glucocorticoid insufficiency.

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